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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/709,045	11/10/2000	M. Rigdon Lentz	LEN 102	3239

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PATREA L. PABST  
HOLLAND & KNIGHT LLP  
SUITE 2000, ONE ATLANTIC CENTER  
1201 WEST PEACHTREE STREET, N.E.  
ATLANTA, GA 30309-3400

EXAMINER	
SEHARASEYON, JEGATHEESAN	
ART UNIT	PAPER NUMBER
1647	14
DATE MAILED: 07/29/2003	

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

<b>Office Action Summary</b>	<b>Application No.</b>		<b>Applicant(s)</b>	
	09/709,045		LENTZ, M. RIGDON	
	<b>Examiner</b>		<b>Art Unit</b>	
	Jegatheesan Seharaseyon		1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 23 March 2003.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-3,5,6,8-11 and 17-22 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3,5,6,8-11 and 17-22 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All   b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                  | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)         | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____                                    |

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### DETAILED ACTION

1. This office action is in response to the amendment and response filed on 4/24/03 in Paper No: 13. Applicant has added claims 17-22. Claims 12-16 were withdrawn from further consideration in the previous Office Action (Paper No: 12). Claims 4 and 7 have been cancelled. Therefore claims 1-3, 5, 6, 8-11 and 17-22 are under consideration.
2. Applicants have amended the priority information.
3. Applicants have amended the summary of the invention.
4. The objection to the disclosure is maintained for reasons indicated in Paper No: 12, page 3, paragraphs 3b and 3c. Correction is required.
5. The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office action.

#### ***Claim Rejections - 35 USC § 112, second paragraph, withdrawn***

6. Applicants amendments to claims 1 and 11, have obviated the previous rejections under 35 U.S.C. 112, second paragraph.

#### ***Claim Rejections - 35 USC § 112, first paragraph, withdrawn***

7. Applicants amendments and arguments have obviated the previous rejections under 35 U.S.C. 112, first paragraph of claims 1, 4, 6, 8 and 11.

#### ***Double Patenting rejection maintained***

8. Applicants arguments have been fully considered but are not deemed persuasive. Regardless of the interpretation of the examiner in the U.S. Patent No. 6,231,536 the claims are directed to removing the soluble cytokine receptor molecules by using an antibody that binds to the soluble cytokine receptor molecules from blood (see claims 5-

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8). Thus the broad claims generically read on the instant invention. Thus the rejection of claims of claims 1-3, 5, 6 and 8-11 are maintained.

### ***Interference***

9. Applicants request declaration of an interference with U.S. Patent No. 6,379,708 (see Page 5 of Paper No: 13). However, Applicant has failed to provide with an explanation why each claim corresponds to the proposed count. Applicant is required to follow the instructions in MPEP 2307 and 37 CFR 1.607 in order to provoke interference.

10. Following are NEW GROUNDS of rejections.

### ***Claim Rejections - 35 USC § 103***

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11a. Claims 1-3, 6, 8-11 and 17-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Selinsky et al. (1998) and Van Zee et al. (1992) in view of Lentz (4,708,713) and further in view of Maraskovsky et al (U.S. Patent (6,017,527).

The claims are directed to a method of reducing the infected tissue in a patient having a pathological condition comprising obtaining blood from the patient and contacting the blood with a recombinant monoclonal or polyclonal antibody or a plurality

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of such which is covalently attached to a column so as to remove TNFR and administering the whole blood into the patient.

Selinsky et al. teach antibodies that are specific for sTNFR I and Ultraphoresis, which is a system that selectively removes plasma components within a defined molecular range. sTNFR I is a potent inhibitor of TNF with the potential to suppress a variety of effector mechanisms important in tumor immunity (see abstract). Selinsky et al also teach that soluble tumor necrosis factor receptor type I is removed by Ultrapheresis (see page 88) and sTNFR I effectively inhibits immune responses *in vivo* and demonstrates that its modulation is a legitimate therapeutic avenue (see page 92). It also describes an anti-human sTNFR I antibody (see page 89). Selinsky et al. also indicates that " We therefore, propose the development of methods and/or reagents capable of specifically removing sTNFR I, or antagonizing its effects *in situ*, as unconventional, yet promising, strategies for cancer immunotherapy." (see page 92). Van Zee et al disclose antibodies for both the sTNFR I and sTNFR II receptors (see abstract and page 4846). Selinsky et al. and Van Zee et al. do not describe the removal of diseased tissue from the blood of a patient for treating diseases and conditions such as cancer and returning the treated blood to the patient to initiate an immune response after removing the soluble cytokine receptors. The reference also does not teach using this method for the treatment of virally induced diseases caused by immunosuppression. In addition, the reference also does not teach a treatment process in which immunosuppressive components in the body are reduced to a level, which allows an acute immune response or until the effects of removing the blocking agents

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become evident in the patient. Selinsky et al. and Van Zee et al. does not teach the separation of plasma prior to Ultrafiltration and returning the treated plasma and blood to the patient. In addition, it also does not teach the removal of immunosuppressive components with a combination of Ultrapheresis and an antibody that is immobilized using standard techniques for binding reactions to remove proteins from the blood. It further does not teach a recombinant monoclonal antibody specific for soluble receptors for tumor necrosis factor that are immobilized to an external device.

Lentz teaches a method and system for removing diseased tissue from the blood of a patient for treating diseases and conditions such as cancer and returning the treated blood to the patient to initiate an immune response (see abstract). Lentz also teaches that the method can treat cancer (including solid tumors) and other diseases including the virally induced AIDS (see column 2, lines 45-50). The treatment process continues until the immunosuppressive components in the body are reduced to a level, which allows an acute immune response or until the effects of removing the blocking agents become evident in the patient (see column 3, lines 50-55). Lentz also contemplates the separation of plasma prior to ultrafiltration and returning the treated plasma and blood to the patient (see column 10, lines 1-10).

Maraskovsky et al. teach a method of stimulating an immune response in a patient providing a method in which antibodies specific to antigens are immobilized onto a surface such as beads (column 4, lines 13-25) and the blood cells are collected by apheresis (see column 3, lines 55-56). The monoclonal antibodies which can be recombinant (column 8, lines 9-25) removes specific cells and the antibody-antigen

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complex is removed by column chromatography method or biological method (column 4, lines 26-49).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the method of Selinsky et al to remove cytokine receptors using antibodies to the cytokine receptors (TNFR I and TNFR II, see Selinsky et al. and Van Zee et al) that inhibit immune response as taught by Lentz for removing diseased tissue to treat cancer and other virally induced diseases, from the blood of a patient with immobilizing the antibodies to the beads to remove the soluble cytokine receptors as taught by Maraskovsky et al.

In addition, one of ordinary skill in the art would have been motivated to with reasonable expectation of success in combining the teachings of Selinsky et al., Van Zee et al., Lentz and Maraskovsky et al. because Selinsky et al. declare that "We, therefore, propose the development of methods and /or reagents capable of specifically removing sTNFR I, or antagonizing its effects *in situ*, as unconventional, yet promising, strategies for cancer immunotherapy." (see page 92). Moreover, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success in combining the teachings of Selinsky et al., Lentz and Maraskovsky et al. because Maraskovsky et al. teach antibodies immobilized on beads for removal of antigens from blood sample. In addition, it would have been obvious to use either a polyclonal antibody or a monoclonal antibody as well as a panel of antibodies that are specific for either one immune system or several immune system inhibitors, for Lentz teaches that there are immunosuppressive components in blood that are separated by Ultrafiltration to

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boost the immune system. In addition, one skilled in the art would know to remove the antibody/antigen complex prior to administering the biological fluid to the patient. Thus, it would have been obvious to use the method of Maraskovsky et al. to immobilize an antibody of Selinsky or Van Zee which specifically binds the sTNFR I or sTNFR II, wherein the sTNFR I or sTNFR II inhibits the immune response, and is removed in the method of Lentz using an immobilized antibody.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

11b. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Selinsky et al. (1998) and Van Zee et al. (1992) in view of Lentz (4,708,713) and further in view of Maraskovsky et al (U.S. Patent (6,017,527) and Feinman et al (1987).

The claims are directed to a method of reducing the infected tissue in a patient having a pathological condition comprising obtaining blood from the patient and contacting the blood with a recombinant monoclonal or polyclonal antibody or a plurality of such which is covalently attached to a column and administering the whole blood into the patient. In the instant invention interferon- $\gamma$  a cytokine is also used in the treatment of blood from the patient.

The relevance of Selinsky et al., Van Zee et al., Lentz and Maraskovsky et al has been set forth above. However, the references do not explicitly recite the use of other compounds/agents for the treatment of cancer tissue by the use of cytokines.



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Feinman et al. discloses the use of interferon- $\gamma$  to increase monocyte cytotoxicity by sensitizing target cells to the lytic action of TNF (see abstract).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time invention was made to modify the methods Selinsky et al., Van Zee et al., Lentz and Maraskovsky et al to contain interferon- $\gamma$ , with a reasonable expectation of success, because Feinman et al. has disclosed that interferon- $\gamma$  increases monocyte cytotoxicity by sensitizing target cells to the lytic action of TNF. Thus, the combination of the removal soluble TNF receptor and sensitizing target cells to the lytic action of TNF by interferon- $\gamma$  will enhance the therapeutic potential. Therefore, the claims are obvious over Selinsky et al. (1998) and Van Zee et al. (1992) in view of Lentz (4,708,713) and further in view of Maraskovsky et al (U.S. Patent (6,017,527) and Feinman et al (1987).

11c. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Selinsky et al. (1998) and Van Zee et al. (1992) in view of Lentz (4,708,713) and further in view of Maraskovsky et al (U.S. Patent (6,017,527) and Goodman et al (U.S. Patent 5,817,522).

The claims are directed to a method of reducing the infected tissue in a patient having a pathological condition comprising obtaining blood from the patient and contacting the blood with a recombinant monoclonal or polyclonal antibody or a plurality of such which is covalently attached to a column and administering the whole blood into the patient. In the instant invention the antibody used is a humanized antibody.

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The relevance of Selinsky et al., Van Zee et al., Lentz and Maraskovsky et al has been set forth above. However, the references do not explicitly recite the use of humanized antibody. Goodman et al. disclose several antibodies including humanized antibodies (column 11, lines 52-65)

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time invention was made to modify the methods Selinsky et al., Van Zee et al., Lentz and Maraskovsky et al to include humanized antibodies in the column, with a reasonable expectation of success, because Goodman et al. has disclosed humanized antibodies as an anti-ligand. Thus, one having ordinary skill in the art would have been motivated to use humanized antibodies to the receptor to remove the soluble receptors from the blood. Therefore, the claims are obvious over Selinsky et al. (1998) and Van Zee et al. (1992) in view of Lentz (4,708,713) and further in view of Maraskovsky et al (U.S. Patent (6,017,527) and Goodman et al (U.S. Patent 5,817,522).

12. No claims are allowable over prior art.

#### **Contact Information**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 703-305-1112. The examiner can normally be reached on M-F: 8:30-4:30.

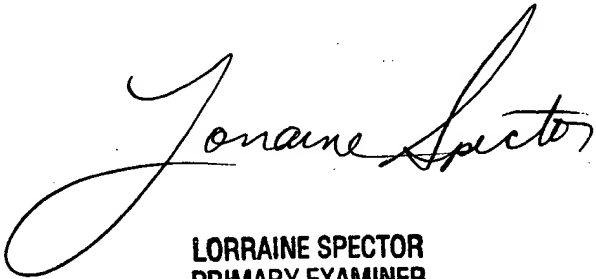
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone numbers for

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the organization where this application or proceeding is assigned are 703-308-0294 for regular communications and 703-308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

js  
July 27, 2003

A handwritten signature in cursive script, reading "Lorraine Spector". The signature is written in black ink and is positioned above the printed name and title.

**LORRAINE SPECTOR  
PRIMARY EXAMINER**